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(54) Title: BIS(THIOHYDRAZIDE AMIDES) FOR INHIBITING ANGIOGENESIS

(57) Abstract: Disclosed herein- are methods of inhibiting angiogenesis in a subject in need thereof with bis(thio-hydrazide amides) represented by a formula selected from Structural Formulas (I)- (IX) or pharmaceutically acceptable salts thereof.

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WO 2008/024298 A1

BIS(THIOHYDRAZIDE AMIDES) FOR INHIBITING ANGIOGENESIS

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Serial No. 60/838,956, filed August 21, 2006, the entire teachings of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Angiogenesis is the growth of new blood vessels, which is an important natural process occurring in the body, both in health and in disease. Angiogenesis occurs in the healthy body for healing wounds and for restoring blood flow to tissues after injury or insult. The healthy body controls angiogenesis through a series of "on" and "off" switches. The main "on" switches are known as angiogenesis-stimulating growth factors. The main "off switches" are known as angiogenesis inhibitors.

When angiogenic growth factors are produced in excess of angiogenesis inhibitors, the balance is tipped in favor of blood vessel growth. When inhibitors are present in excess of stimulators, angiogenesis is stopped. The normal, healthy body maintains a balance of angiogenesis modulators.

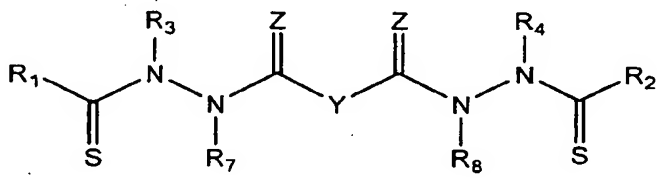
However, in many serious diseases states, the body looses control over angiogenesis. Angiogenesis-dependent diseases result when new blood vessels either grow excessively or insufficiently.

Excessive angiogenesis occurs in diseases such as cancer, diabetic blindness, age-related macular degeneration, rheumatoid arthritis, psoriasis, and more than 70 other conditions. In these conditions, new blood vessels feed diseased tissues, destroy normal tissues, and in the case of cancer, the new vessels allow tumor cells to escape into the circulation and lodge in other organs (tumor metastases). Excessive angiogenesis occurs when diseased cells produce abnormal amounts of angiogenic growth factors, overwhelming the effects of natural angiogenesis inhibitors.

It is estimated that at least 184 million patients in Western nations could benefit from some form of anti-angiogenetic therapy.

SUMMARY OF THE INVENTION

Disclosed are methods employing bis(thio-hydrazide amides) to inhibit angiogenesis in a subject in need thereof. The methods include administering to the subject an effective amount of a bis(thio-hydrazide amide) represented by Structural Formula I:



I

Y is a covalent bond or an optionally substituted straight chained hydrocarbyl group, or, Y, taken together with both >C=Z groups to which it is bonded, is an optionally substituted aromatic group.

R_1-R_4 are independently -H, an optionally substituted aliphatic group, an optionally substituted aryl group, or R_1 and R_3 taken together with the carbon and nitrogen atoms to which they are bonded, and/or R_2 and R_4 taken together with the carbon and nitrogen atoms to which they are bonded, form a non-aromatic ring optionally fused to an aromatic ring.

R_7-R_8 are independently -H, an optionally substituted aliphatic group, or an optionally substituted aryl group.

Z is O or S.

Also disclosed are methods of treating a subject with a condition selected from the group consisting of ocular neovascular disease, macular degeneration (e.g., age-related); corneal graft rejection; neovascular glaucoma; retrolental fibroplasias; epidemic keratoconjunctivitis; Vitamin A deficiency; contact lens overwear; atopic keratitis; superior limbic keratitis; pterygium keratitis sicca; sjogrens; acne; rosacea; wartsphylectenulosis; lipid degeneration; chemical burns; Terrien's marginal degeneration; mariginal keratolysis; rheumatoid arthritis; polyarteritis; Wegener's sarcoidosis; scleritis; Stevens-Johnson disease; pemphigoid; radial keratotomy; corneal graph rejection; sickle cell anemia; sarcoid; pseudoxanthoma elasticum; Paget's disease; vein occlusion; carotid obstructive disease; chronic uveitis/vitritis; Eales' disease; Behcet's disease; infections causing a retinitis or choroiditis; presumed ocular histoplasmosis; Best's disease; myopia; optic pits; Stargardt's disease; pars planitis; chronic retinal detachment; hyperviscosity syndromes; diseases associated

with rubeosis (neovascularization of the angle); osteoarthritis; ulcerative colitis; Crohn's disease; BartonellosisOsler-Weber-Rendu disease; hereditary hemorrhagic telangiectasia; pulmonary hemangiomatosis; pre-eclampsia; fibrosis of the liver and of the kidney; developmental abnormalities (organogenesis); skin disclolorations (*e.g.*, hemangioma, nevus flammeus, or nevus simplex); hypertrophic scars, *i.e.*, keloids; wound granulation; vascular adhesions; cat scratch disease (Rochele ninalia quintosa); keratoconjunctivitis; gingivitis; epulis; tonsillitis; obesity; laryngitis; tracheitis; bronchiolitis; pulmonary edema; neurodermitis; thyroiditis; thyroid enlargement; glomerulonephritis; gastritis; inflammatory bone and cartilage destruction; thromboembolic disease; and Buerger's disease, comprising administering to the subject an effective amount of a compound represented represented by Structural Formula **I**.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to methods of inhibiting angiogenesis in a subject in need thereof with an effective amount of a bis(thio-hydrazide amide) represented by a formula selected from Structural Formulas (I)- (IX) (or a compound encompassed by these structural formulas) or a pharmaceutically acceptable salt thereof, pharmaceutical compositions comprising these bis(thio-hydrazide amides) and compositions comprising these bis(thiohydrazide)amides and an additional pharmaceutically active agent(s). In one aspect, the subject is human.

Yet another embodiment of the present invention is the use of a bis(thiohydrazide amide) disclosed herein for the manufacture of a medicament for inhibiting angiogenesis in a subject in need thereof or for treating ocular neovascular disease, macular degeneration (e.g., age-related); corneal graft rejection; neovascular glaucoma; retrolental fibroplasias; epidemic keratoconjunctivitis; Vitamin A deficiency; contact lens overwear; atopic keratitis; superior limbic keratitis; pterygium keratitis sicca; sjogrens; acne; rosacea; wartsphylectenulosis; lipid degeneration; chemical burns; Terrien's marginal degeneration; mariginal keratolysis; rheumatoid arthritis; polyarteritis; Wegener's sarcoidosis; scleritis; Stevens-Johnson disease; pemphigoid; radial keratotomy; corneal graph rejection; sickle cell anemia; sarcoid;

pseudoxanthoma elasticum; Paget's disease; vein occlusion; carotid obstructive disease; chronic uveitis/vitritis; Eales' disease; Behcet's disease; infections causing a retinitis or choroiditis; presumed ocular histoplasmosis; Best's disease; myopia; optic pits; Stargardt's disease; pars planitis; chronic retinal detachment; hyperviscosity syndromes; diseases associated with rubeosis (neovascularlation of the angle); osteoarthritis; ulcerative colitis; Crohn's disease; BartonellosisOsler-Weber-Rendu disease; hereditary hemorrhagic telangiectasia; pulmonary hemangiomatosis; pre-eclampsia; fibrosis of the liver and of the kidney; developmental abnormalities (organogenesis); skin disclolorations (*e.g.*, hemangioma, nevus flammeus, or nevus simplex); hypertrophic scars, *i.e.*, keloids; wound granulation; vascular adhesions; cat scratch disease (Rochele ninalia quintosa); keratoconjunctivitis; gingivitis; epulis; tonsillitis; obesity; laryngitis; tracheitis; bronchiolitis; pulmonary edema; neurodermitis; thyroiditis; thyroid enlargement; glomerulonephritis; gastritis; inflammatory bone and cartilage destruction; thromboembolic disease; or Buerger's disease in a subject.

Angiogenesis can be divided into the following types:

Sprouting Angiogenesis

Sprouting angiogenesis is a process resulting in the formation of entirely new vessels.

Intussusceptive Angiogenesis

Intussusception, is known as splitting angiogenesis. In this type of vessel formation, existing vessels are split rather than the formation of entirely new vessel as with sprouting angiogenesis.

The present invention encompasses methods of treating both types of angiogenesis.

Conditions which are characterized by excessive or abnormal growth of new blood vessels and which can be treated with the disclosed bis(thiohydrazide amides) include ocular neovascular disease, macular degeneration (e.g., age-related); corneal graft rejection; neovascular glaucoma; retrolental fibroplasias; epidemic keratoconjunctivitis; Vitamin A deficiency; contact lens overwear; atopic keratitis; superior limbic keratitis; pterygium keratitis sicca; sjogrens; acne; rosacea; wartsphylectenulosis; lipid degeneration; chemical burns; Terrien's marginal

degeneration; mariginal keratolysis; rheumatoid arthritis; polyarteritis; Wegener's sarcoidosis; scleritis; Stevens-Johnson disease; pemphigoid; radial keratotomy; corneal graph rejection; sickle cell anemia; sarcoid; pseudoxanthoma elasticum; Paget's disease; vein occlusion; carotid obstructive disease; chronic uveitis/vitritis; Eales' disease; Behcet's disease; infections causing a retinitis or choroiditis; presumed ocular histoplasmosis; Best's disease; myopia; optic pits; Stargardt's disease; pars planitis; chronic retinal detachment; hyperviscosity syndromes; diseases associated with rubeosis (neovascularization of the angle); osteoarthritis; ulcerative colitis; Crohn's disease; BartonellosisOsler-Weber-Rendu disease; hereditary hemorrhagic telangiectasia; pulmonary hemangiomatosis; pre-eclampsia; fibrosis of the liver and of the kidney; developmental abnormalities (organogenesis); skin disclolorations (*e.g.*, hemangioma, nevus flammeus, or nevus simplex); hypertrophic scars, *i.e.*, keloids; wound granulation; vascular adhesions; cat scratch disease (Rochele ninalia quintosa); keratoconjunctivitis; gingivitis; epulis; tonsillitis; obesity; laryngitis; tracheitis; bronchiolitis; pulmonary edema; neurodermitis; thyroiditis; thyroid enlargement; glomerulonephritis; gastritis; inflammatory bone and cartilage destruction; thromboembolic disease; and Buerger's disease.

Other conditions characterized by excessive or abnormal growth of new blood vessels and which can be treated with the disclosed bis(thiohydrazide amides) include ocular neovascular disease, macular degeneration (e.g., age-related); neovascular glaucoma; acne; rosacea;; lipid degeneration; rheumatoid arthritis; polyarteritis; Wegener's sarcoidosis; scleritis; Stevens-Johnson disease; pemphigoid; radial keratotomy; sickle cell anemia; sarcoid; pseudoxanthoma elasticum; Paget's disease; vein occlusion; chronic uveitis/vitritis; Eales' disease; Behcet's disease; Best's disease; myopia; Stargardt's disease; diseases associated with rubeosis (neovascularization of the angle); osteoarthritis; ulcerative colitis; Crohn's disease; BartonellosisOsler-Weber-Rendu disease; hereditary hemorrhagic telangiectasia; pulmonary hemangiomatosis; pre-eclampsia; keratoconjunctivitis; gingivitis; tonsillitis; obesity; laryngitis; tracheitis; bronchiolitis; pulmonary edema; neurodermitis; thyroiditis; thyroid enlargement; glomerulonephritis; gastritis; thromboembolic disease; and Buerger's disease.

Other conditions characterized by excessive or abnormal growth of new blood vessels and which can be treated with the disclosed bis(thiohydrazide amides) include macular degeneration, acne, rosacea, rheumatoid arthritis, sickle cell anemia, myopia, toxoplasmosis, osteoarthritis, Crohn's disease, pre-eclampsia, obesity, laryngitis, pulmonary edema and glomerulonephritis.

In certain embodiment the present invention is directed to methods of treating or inhibiting angiogenesis in a subject with a condition selected from the group consisting of as acne, rosacea, rheumatoid arthritis, osteoarthritis, Crohn's disease and obesity with a bis(thio-hydrazide amide).

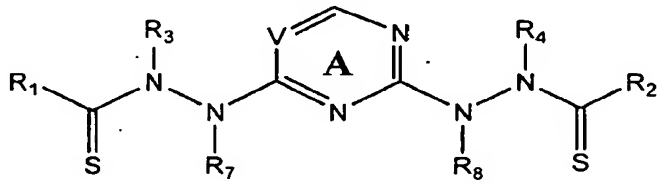
In certain embodiments the methods of the present invention does not include treating subjects suffering from a condition selected from the group diabetic retinopathy, retinopathy of prematurity, systemic lupus, mycobacteria infections, bacterial ulcers; fungal ulcers; Herpes simplex infections; Herpes zoster infections; protozoan infections toxoplasmosis diseases caused by the abnormal proliferation of fibrovascular or fibrous tissue including all forms of proliferative vitreoretinopathy, interstitial pulmonary fibrosis, eczema; syphilis, Kaposi's sarcoma, trauma, trauma and post-laser complications; artery occlusion, atherosclerosis; endometriosis, wound healing, ulcers (Helicobacter pylori), Mooren's ulcer; periodontal disease, hepatitis, rhinitis, bronchitis, pneumonia, and cancer.

The bis(thio-hydrazide amides) employed in the disclosed invention are represented by Structural Formula I and pharmaceutically acceptable salts and solvates of the compounds represented by Structural Formula I.

In one embodiment, Y in Structural Formula I is a covalent bond, -$C(R_5R_6)$-, -(CH_2CH_2)-, trans-(CH=CH)-, cis-(CH=CH)- or –(C≡C)- group, preferably -$C(R_5R_6)$-. R_1-R_4 are as described above for Structural Formula I. R_5 and R_6 are each independently -H, an aliphatic or substituted aliphatic group, or R_5 is -H and R_6 is an optionally substituted aryl group, or, R_5 and R_6, taken together, are an optionally substituted C2-C6 alkylene group. In one embodiment, the compound of Structural Formula I is in the form of a pharmaceutically acceptable salt. In one embodiment, the compound of Structural Formula I is in the form of a pharmaceutically acceptable

salt in combination with one or more pharmaceutically acceptable cations. The pharmaceutically acceptable cations are as described in detail below.

In specific embodiments, Y taken together with both >C=Z groups to which it is bonded, is an optionally substituted aromatic group. In this instance, certain bis(thio-hydrazide amides) are represented by Structural Formula **II**:

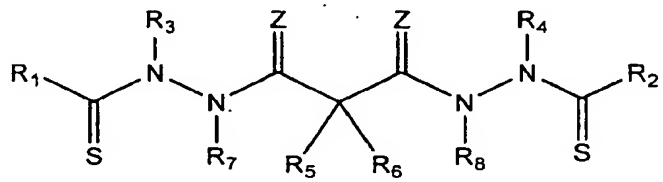


II

;

wherein Ring A is substituted or unsubstituted and V is –CH- or –N-. The other variables in Structural Formula **II** are as described herein for Structural Formula **I** or **IIIa**.

In particular embodiments, the bis(thio-hydrazide amides) are represented by Structural Formula **IIIa**:



IIIa

R_1-R_8 are as described above for Structural Formula **I**.

In Structural Formulas **I-IIIa**, R_1 and R_2 are the same or different and/or R_3 and R_4 are the same or different; preferably, R_1 and R_2 are the same and R_3 and R_4 are the same. In Structural Formulas **I** and **IIIa**, Z is preferably O. Typically in Structural Formulas **I** and **IIIa**, Z is O; R_1 and R_2 are the same; and R_3 and R_4 are the same. More preferably, Z is O; R_1 and R_2 are the same; R_3 and R_4 are the same, and R_7 and R_8 are the same.

In other embodiments, the bis(thio-hydrazide amides) are represented by Structural Formula **IIIa**: R_1 and R_2 are each an optionally substituted aryl group, preferably an optionally substituted phenyl group; R_3 and R_4 are each an optionally substituted aliphatic group, preferably an alkyl group optionally substituted with -OH, halogen, phenyl, benzyl, pyridyl, or C1-C8 alkoxy and R_6 is -H or methyl, more preferably, methyl or ethyl group optionally substituted with -OH, halogen, phenyl, benzyl, pyridyl, or C1-C8 alkoxy and R_6 is -H or methyl optionally substituted with

-OH, halogen or C1-C4 alkoxy; and R_5 and R_6 are as described above, but R_5 is preferably –H and R_6 is preferably –H, an aliphatic or substituted aliphatic group.

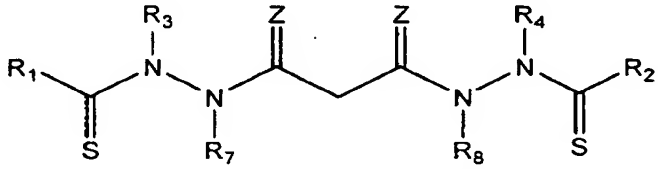
Alternatively, R_1 and R_2 are each an optionally substituted aryl group; R_3 and R_4 are each an optionally substituted aliphatic group; R_5 is -H; and R_6 is -H, an aliphatic or substituted aliphatic group. Preferably, R_1 and R_2 are each an optionally substituted aryl group; R_3 and R_4 are each an alkyl group optionally substituted with -OH, halogen, phenyl, benzyl, pyridyl, or C1-C8 alkoxy and R_6 is -H or methyl; and R_5 is -H and R_6 is -H or methyl. Even more preferably, R_1 and R_2 are each an optionally substituted phenyl group, preferably optionally substituted with -OH, halogen, C1-4 alkyl or C1-C4 alkoxy; R_3 and R_4 are each methyl or ethyl optionally substituted with -OH, halogen or C1-C4 alkoxy; and R_5 is -H and R_6 is -H or methyl. Suitable substituents for an aryl group represented by R_1 and R_2 and an aliphatic group represented by R_3, R_4 and R_6 are as described below for aryl and aliphatic groups.

In another embodiment, the bis(thio-hydrazide amides) are represented by Structural Formula **IIIa**: R_1 and R_2 are each an optionally substituted aliphatic group, preferably a C3-C8 cycloalkyl group optionally substituted with at least one alkyl group, more preferably cyclopropyl or 1-methylcyclopropyl; R_3 and R_4 are as described above for Structural Formula **I**, preferably both an optionally substituted alkyl group; and R_5 and R_6 are as described above, but R_5 is preferably –H and R_6 is preferably –H, an aliphatic or substituted aliphatic group, more preferably –H or methyl.

Alternatively, the bis(thio-hydrazide amides) are represented by Structural Formula **IIIa**: R_1 and R_2 are each an optionally substituted aliphatic group; R_3 and R_4 are as described above for Structural Formula **I**, preferably both an optionally substituted alkyl group; and R_5 is –H and R_6 is –H or an optionally substituted aliphatic group. Preferably, R_1 and R_2 are both a C3-C8 cycloalkyl group optionally substituted with at least one alkyl group; R_3 and R_4 are both as described above for Structural Formula **I**, preferably an alkyl group; and R_5 is –H and R_6 is –H or an aliphatic or substituted aliphatic group. More preferably, R_1 and R_2 are both a C3-C8 cycloalkyl group optionally substituted with at least one alkyl group; R_3 and R_4 are both an alkyl group optionally substituted with -OH, halogen, phenyl, benzyl, pyridyl, or C1-C8 alkoxy and R_6 is -H or methyl; and R_5 is –H and R_6 is –H or methyl. Even

more preferably, R_1 and R_2 are both cyclopropyl or 1-methylcyclopropyl; R_3 and R_4 are both an alkyl group, preferably methyl or ethyl optionally substituted with -OH, halogen or C1-C4 alkoxy; and R_5 is –H and R_6 is –H or methyl.

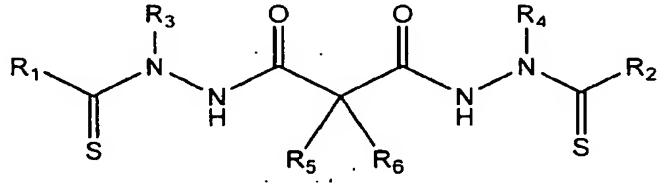
In particular embodiments, the bis(thio-hydrazide amides) are represented by Structural Formula **IIIb**:



IIIb

wherein R_1, R_2, R_3, R_4, R_7, R_8, and Z are as defined above for Structural Formula **IIIa**.

In specific embodiments, the bis(thio-hydrazide amides) are represented by Structural Formula **IVa**:



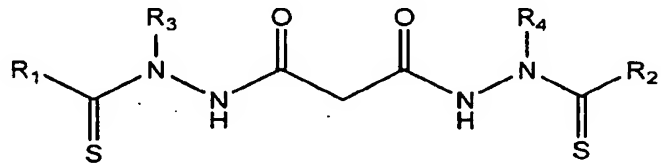
IVa

wherein: R_1 and R_2 are both phenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both phenyl, R_3 and R_4 are both ethyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 4-cyanophenyl, R_3 and R_4 are both methyl, R_5 is methyl, and R_6 is -H; R_1 and R_2 are both 4-methoxyphenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both phenyl, R_3 and R_4 are both methyl, R_5 is methyl, and R_6 is -H; R_1 and R_2 are both phenyl, R_3 and R_4 are both ethyl, R_5 is methyl, and R_6 is -H; R_1 and R_2 are both 4-cyanophenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 2,5-dimethoxyphenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 2,5-dimethoxyphenyl, R_3 and R_4 are both methyl, R_5 is methyl, and R_6 is -H; R_1 and R_2 are both 3-cyanophenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 3-fluorophenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 4-chlorophenyl, R_3 and R_4 are both methyl, R_5 is methyl, and R_6 is -H; R_1 and R_2 are both 2-dimethoxyphenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 3-methoxyphenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are

both -H; R_1 and R_2 are both 2,3-dimethoxyphenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 2,3-dimethoxyphenyl, R_3 and R_4 are both methyl, R_5 is methyl, and R_6 is -H; R_1 and R_2 are both 2,5-difluorophenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 2,5-difluorophenyl, R_3 and R_4 are both methyl, R_5 is methyl, and R_6 is -H; R_1 and R_2 are both 2,5-dichlorophenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 2,5-dimethylphenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 2,5-dimethoxyphenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both phenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 2,5-dimethoxyphenyl, R_3 and R_4 are both methyl, R_5 is methyl, and R_6 is -H; R_1 and R_2 are both cyclopropyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both cyclopropyl, R_3 and R_4 are both ethyl, and R_5 and R_6 are both -H; R_1 and R_2 are both cyclopropyl, R_3 and R_4 are both methyl, R_5 is methyl, and R_6 is -H; R_1 and R_2 are both 1-methylcyclopropyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 1-methylcyclopropyl, R_3 and R_4 are both methyl, R_5 is methyl and R_6 is -H; R_1 and R_2 are both 1-methylcyclopropyl, R_3 and R_4 are both methyl, R_5 is ethyl, and R_6 is -H; R_1 and R_2 are both 1-methylcyclopropyl, R_3 and R_4 are both methyl, R_5 is *n*-propyl, and R_6 is -H; R_1 and R_2 are both 1-methylcyclopropyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both methyl; R_1 and R_2 are both 1-methylcyclopropyl, R_3 and R_4 are both ethyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 1-methylcyclopropyl, R_3 is methyl, R_4 is ethyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 2-methylcyclopropyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 2-phenylcyclopropyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 1-phenylcyclopropyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both cyclobutyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both cyclopentyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both cyclohexyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both cyclohexyl, R_3 and R_4 are both phenyl, and R_5 and R_6 are both -H; R_1 and R_2 are both methyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both methyl, R_3 and R_4 are both *t*-butyl, and R_5 and R_6 are both -H; R_1 and R_2 are both methyl, R_3 and R_4 are both phenyl, and R_5 and R_6 are both -H; R_1 and

R_2 are both *t*-butyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are ethyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; or R_1 and R_2 are both *n*-propyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H.

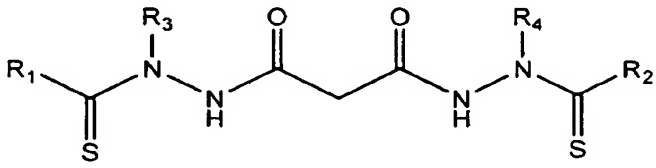
In particular embodiments, the bis(thio-hydrazide amides) are represented by Structural Formula **IVb**:



IVb

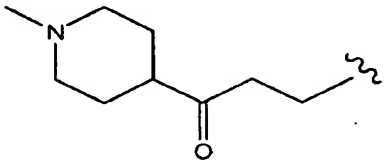
wherein R_1, R_2, R_3, and R_4 are as defined above for Structural Formula **IVa**.

In specific embodiments, the bis(thio-hydrazide amides) are represented by Structural Formula **V**:



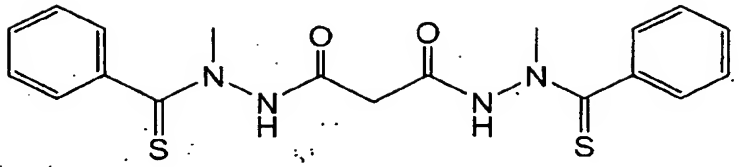
V

wherein: R_1 and R_2 are both phenyl, and R_3 and R_4 are both *o*-CH_3-phenyl; R_1 and R_2 are both *o*-$CH_3C(O)O$-phenyl, and R_3 and R_4 are phenyl; R_1 and R_2 are both phenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both phenyl, and R_3 and R_4 are both ethyl; R_1 and R_2 are both phenyl, and R_3 and R_4 are both *n*-propyl; R_1 and R_2 are both *p*-cyanophenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both *p*-nitro phenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 2,5-dimethoxyphenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both phenyl, and R_3 and R_4 are both *n*-butyl; R_1 and R_2 are both *p*-chlorophenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 3-nitrophenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 3-cyanophenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 3-fluorophenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 2-furanyl, and R_3 and R_4 are both phenyl; R_1 and R_2 are both 2-methoxyphenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 3-methoxyphenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 2,3-dimethoxyphenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 2-methoxy-5-chlorophenyl, and R_3 and R_4 are both ethyl; R_1 and R_2 are both 2,5-difluorophenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both

2,5-dichlorophenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 2,5-dimethylphenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 2-methoxy-5-chlorophenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 3,6-dimethoxyphenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both phenyl, and R_3 and R_4 are both 2-ethylphenyl; R_1 and R_2 are both 2-methyl-5-pyridyl, and R_3 and R_4 are both methyl; or R_1 is phenyl; R_2 is 2,5-dimethoxyphenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both methyl, and R_3 and R_4 are both *p*-CF_3-phenyl; R_1 and R_2 are both methyl, and R_3 and R_4 are both *o*-CH_3-phenyl; R_1 and R_2 are both –$(CH_2)_3COOH$; and R_3 and R_4 are both phenyl; R_1 and R_2 are both represented by the following structural formula: 

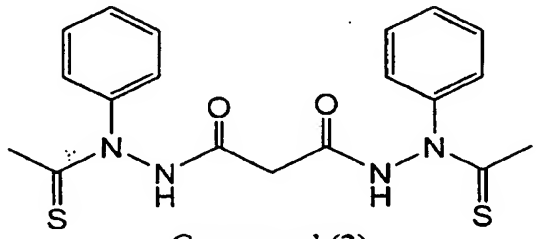
,and R_3 and R_4 are both phenyl; R_1 and R_2 are both *n*-butyl, and R_3 and R_4 are both phenyl; R_1 and R_2 are both *n*-pentyl, R_3 and R_4 are both phenyl; R_1 and R_2 are both methyl, and R_3 and R_4 are both 2-pyridyl; R_1 and R_2 are both cyclohexyl, and R_3 and R_4 are both phenyl; R_1 and R_2 are both methyl, and R_3 and R_4 are both 2-ethylphenyl; R_1 and R_2 are both methyl, and R_3 and R_4 are both 2,6-dichlorophenyl; R_1-R_4 are all methyl; R_1 and R_2 are both methyl, and R_3 and R_4 are both *t*-butyl; R_1 and R_2 are both ethyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both *t*-butyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both cyclopropyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both cyclopropyl, and R_3 and R_4 are both ethyl; R_1 and R_2 are both 1-methylcyclopropyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 2-methylcyclopropyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 1-phenylcyclopropyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 2-phenylcyclopropyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both cyclobutyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both cyclopentyl, and R_3 and R_4 are both methyl; R_1 is cyclopropyl, R_2 is phenyl, and R_3 and R_4 are both methyl.

Preferred examples of bis(thio-hydrazide amides) include Compounds (1)-(18) and pharmaceutically acceptable salts and solvates thereof:



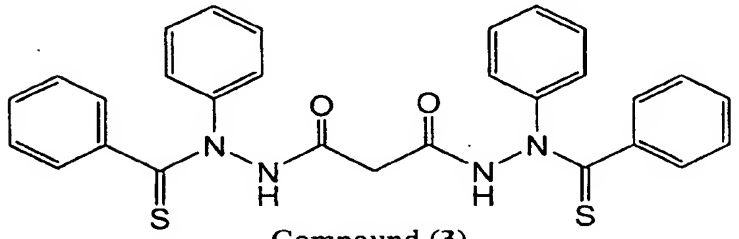
Compound (1)

;



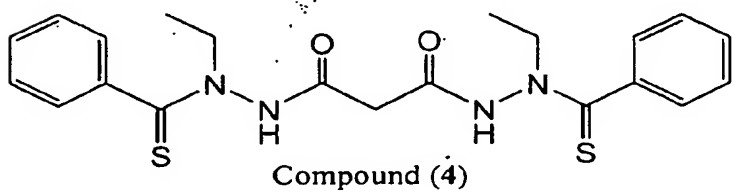
Compound (2)

;



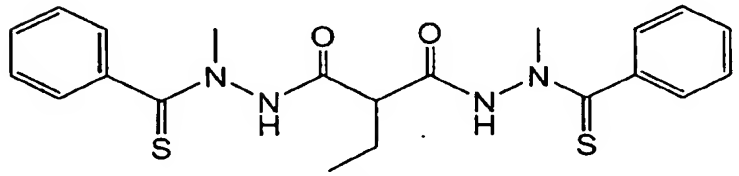
Compound (3)

;



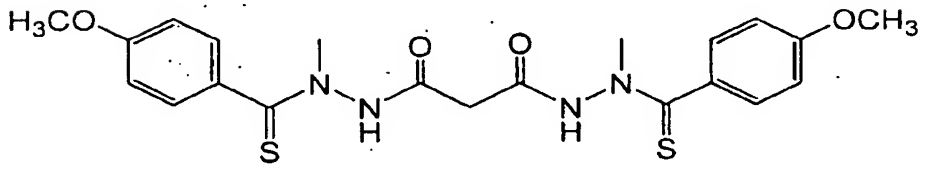
Compound (4)

;



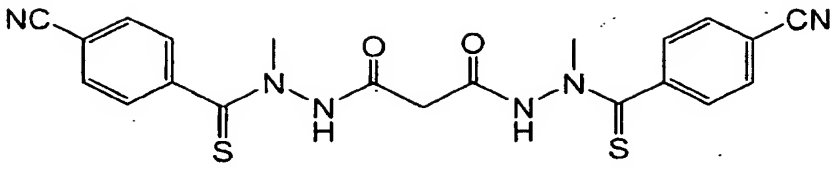
Compound (5)

;



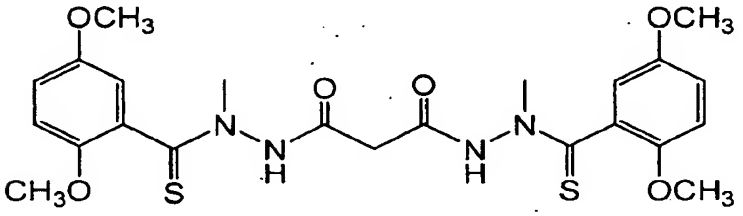
Compound (6)

;



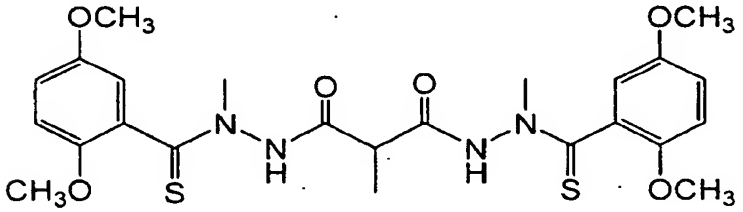
Compound (7)

;



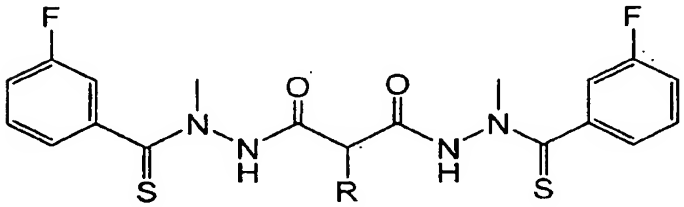
Compound (8)

;



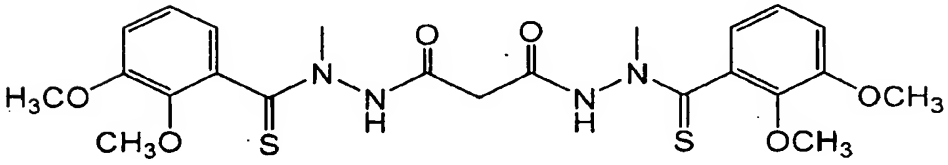
Compound (9)

;



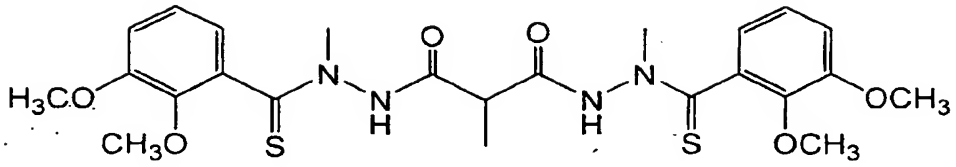
Compound (10)

;



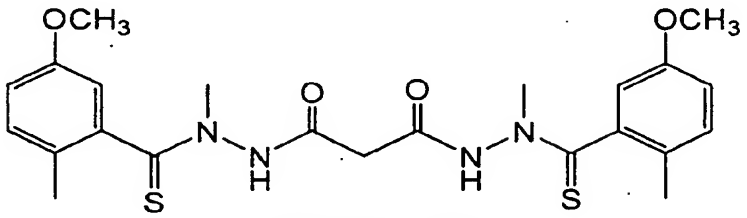
Compound (11)

;



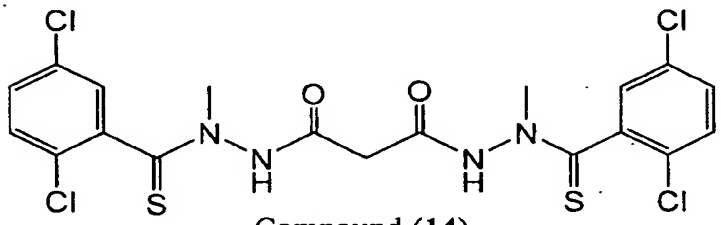
Compound (12)

;



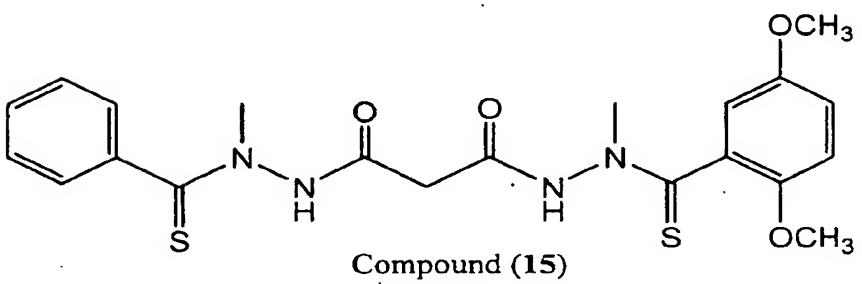
Compound (13)

;



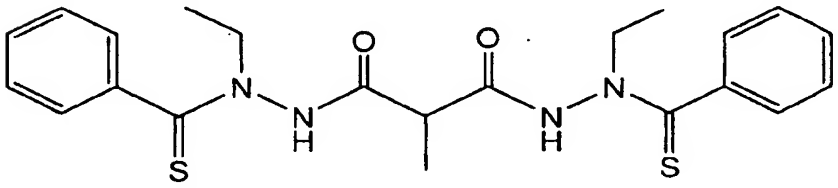
Compound (14)

;



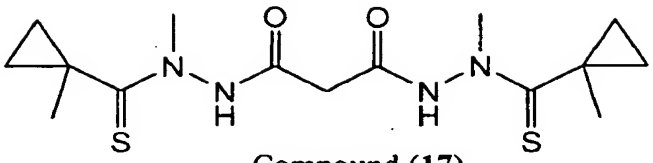
Compound (15)

;

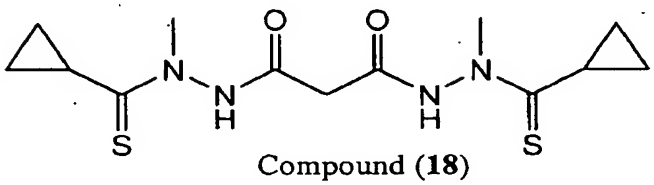


Compound (16)

;



Compound (**17**) ; and



Compound (**18**)

As used herein, the term "bis(thio-hydrazide amide)" and references to the Structural Formulas of this invention also include pharmaceutically acceptable salts and solvates of these compounds and Structural Formulas. Examples of acceptable salts and solvates are described in US Publication No.: 20060135595 and US Patent Application Serial No.: 11/432,307 filed 11-May-2006, titled Synthesis Of Bis(Thio-Hydrazide Amide) Salts, the entire contents of each of which are incorporated herein by reference.

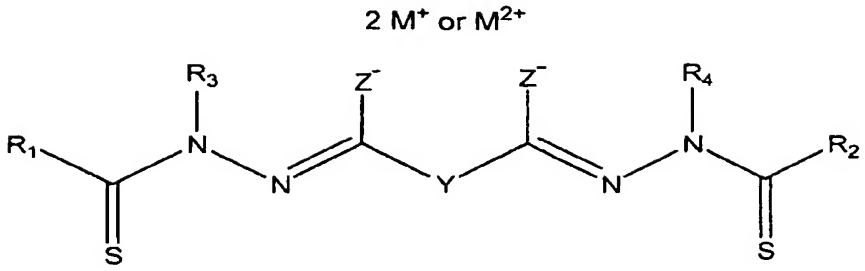
These compounds can have one or more sufficiently acidic proton that can react with a suitable organic or inorganic base to form a base addition salt. Base addition salts include those derived from inorganic bases, such as ammonium or alkali or alkaline earth metal hydroxides, carbonates, bicarbonates, and the like, and organic bases such as alkoxides, alkyl amides, alkyl and aryl amines, and the like. Such bases useful in preparing the salts of this invention thus include sodium hydroxide, potassium hydroxide, ammonium hydroxide, potassium carbonate, and the like.

For example, pharmaceutically acceptable salts of bis(thio-hydrazide) amides employed herein (*e.g.*, those represented by Structural Formulas I-V and Compounds 1-18) are those formed by the reaction of the compound with one equivalent of a suitable base to form a monovalent salt (*i.e.*, the compound has single negative charge that is balanced by a pharmaceutically acceptable counter cation, *e.g.*, a monovalent cation) or with two equivalents of a suitable base to form a divalent salt (*e.g.*, the compound has a two-electron negative charge that is balanced by two pharmaceutically acceptable counter cations, *e.g.*, two pharmaceutically acceptable monovalent cations or a single pharmaceutically acceptable divalent cation). Divalent

salts of the bis(thio-hydrazide amides) are preferred. "Pharmaceutically acceptable" means that the cation is suitable for administration to a subject. Examples include Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+} and NR_4^+, wherein each R is independently hydrogen, an optionally substituted aliphatic group (*e.g.*, a hydroxyalkyl group, aminoalkyl group or ammoniumalkyl group) or optionally substituted aryl group, or two R groups, taken together, form an optionally substituted non-aromatic heterocyclic ring optionally fused to an aromatic ring. Generally, the pharmaceutically acceptable cation is Li^+, Na^+, K^+, $NH_3(C_2H_5OH)^+$ or $N(CH_3)_3(C_2H_5OH)^+$, and more typically, the salt is a disodium or dipotassium salt, preferably the disodium salt.

Bis(thio-hydrazide) amides employed herein having a sufficiently basic group, such as an amine can react with an organic or inorganic acid to form an acid addition salt. Acids commonly employed to form acid addition salts from compounds with basic groups are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenyl-sulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like. Examples of such salts include the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, gamma-hydroxybutyrate, glycolate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate, and the like.

Salts of the disclosed bis(thiohydrazide amides) may have tautomeric forms. By way of example, one tautomeric form for the disalt is is:



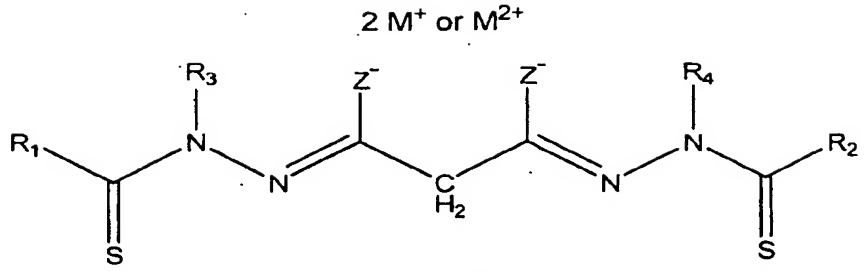
(VI)

Y is a covalent bond or a substituted or unsubstituted straight chained hydrocarbyl group. R_1-R_4 are independently -H, an aliphatic group, a substituted aliphatic group, an aryl group or a substituted aryl group, or R_1 and R_3 taken together with the carbon and nitrogen atoms to which they are bonded, and/or R_2 and R_4 taken together with the carbon and nitrogen atoms to which they are bonded, form a non-aromatic heterocyclic ring optionally fused to an aromatic ring. Z is -O or –S. M^+ is a pharmaceutically acceptable monovalent cation and M^{2+} is a pharmaceutically acceptable divalent cation.

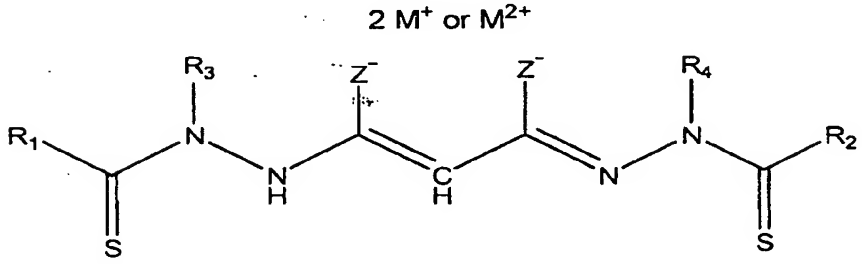
In one embodiment, the variables for Structural Formula (VI) are defined below:

M^+ is a pharmaceutically acceptable monovalent cation. M^{2+} is a pharmaceutically acceptable divalent cation. "Pharmaceutically acceptable" means that the cation is suitable for administration to a subject. Examples of M^+ or M^{2+} include Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Zn^{2+}, and NR_4^+, wherein each R is independently hydrogen, a substituted or unsubstituted aliphatic group (e.g., a hydroxyalkyl group, aminoalkyl group or ammoniumalkyl group) or substituted or unsubstituted aryl group, or two R groups, taken together, form a substituted or unsubstituted non-aromatic heterocyclic ring optionally fused to an aromatic ring. Preferably, the pharmaceutically acceptable cation is Li^+, Na^+, K^+, $NH_3(C_2H_5OH)^+$, $N(CH_3)_3(C_2H_5OH)^+$, arginine or lysine. More preferably, the pharmaceutically acceptable cation is Na^+ or K^+. Na^+ is even more preferred.

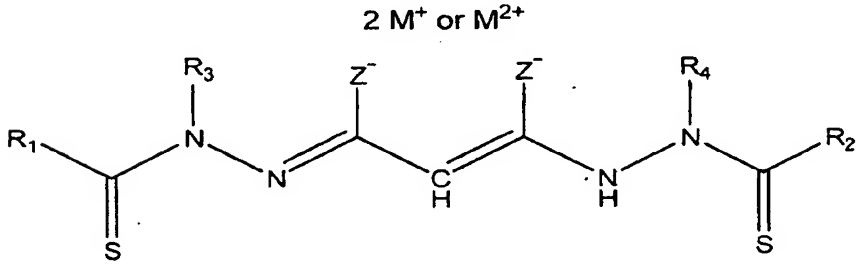
Exemplary tautomeric forms of the disalt compounds represented by Structural Formula (VI) wherein Y is $–CH_2-$ are shown below:



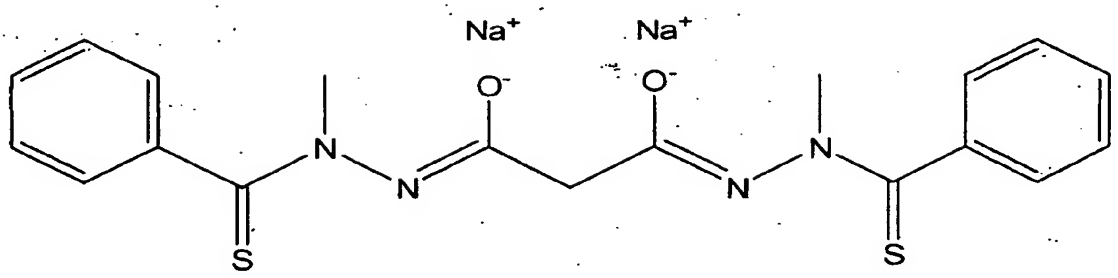
;

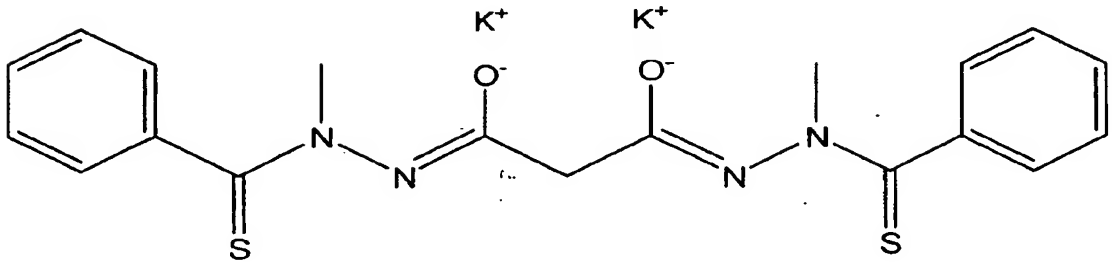


; and

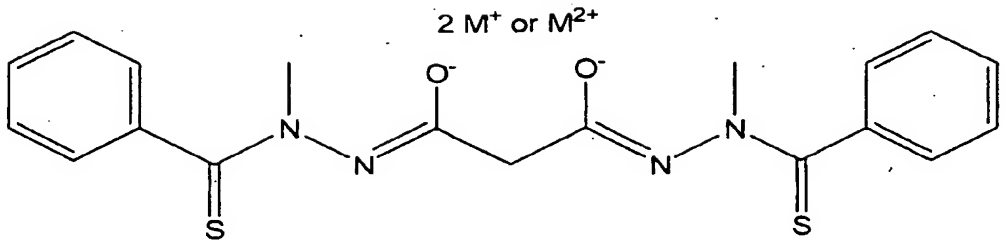


Representative tautomeric structures of the disalt of Compound (1) are shown below:

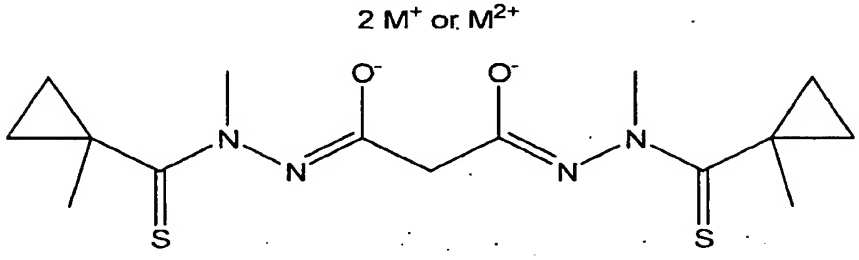




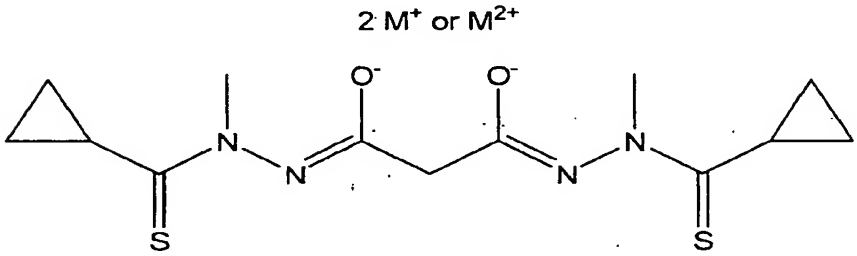
Preferred examples of bis(thio-hydrazide amide) disalts of the present invention are the following:



(VI);



(VIII); and



(IX).

$2\ M^+$ and M^{2+} are as described above for Structural Formula (VI). Preferably, the pharmaceutically acceptable cation is $2\ M^+$, wherein M^+ is Li^+, Na^+, K^+, $NH_3(C_2H_5OH)^+$ or $N(CH_3)_3(C_2H_5OH)^+$. More preferably, M^+ is Na^+ or K^+. Even more preferably, M^+ is Na^+.

It is to be understood when one tautomeric form of a disclosed compound is depicted structurally, other tautomeric forms are also encompassed.

Certain compounds of the invention may be obtained as different stereoisomers (e.g., diastereomers and enantiomers). The invention includes all isomeric forms and racemic mixtures of the disclosed compounds and methods of treating a subject with both pure isomers and mixtures thereof, including racemic mixtures. Stereoisomers can be separated and isolated using any suitable method, such as chromatography.

An "alkyl group" is saturated straight or branched chain linear or cyclic hydrocarbon group. Typically, a straight chained or branched alkyl group has from 1 to about 20 carbon atoms, preferably from 1 to about 10, and a cyclic alkyl group has

from 3 to about 10 carbon atoms, preferably from 3 to about 8. An alkyl group is preferably a straight chained or branched alkyl group, e.g, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *tert*-butyl, pentyl, hexyl, pentyl or octyl, or a cycloalkyl group with 3 to about 8 carbon atoms. A C1-C8 straight chained or branched alkyl group or a C3-C8 cyclic alkyl group is also referred to as a "lower alkyl" group. Suitable substitutents for an alkyl group are those which do not substantially interfere with the biological activity of the disclosed compounds. Suitable substituents are as described below for aliphatic groups. Preferred substituents on alkyl groups include, -OH, $-NH_2$, $-NO_2$, -CN, -COOH, halogen, aryl, C1-C8 alkoxy, C1-C8 haloalkoxy and –CO(C1-C8 alkyl). More preferred substituents on alkyl groups include -OH, halogen, phenyl, benzyl, pyridyl, and C1-C8 alkoxy. More preferred substituents on alkyl groups include -OH, halogen, and C1-C4 alkoxy.

A "straight chained hydrocarbyl group" is an alkylene group, i.e., $-(CH_2)_y-$, with one or more (preferably one) internal methylene groups optionally replaced with a linkage group. y is a positive integer (e.g., between 1 and 10), preferably between 1 and 6 and more preferably 1 or 2. A "linkage group" refers to a functional group which replaces a methylene in a straight chained hydrocarbyl. Examples of suitable linkage groups include a ketone (-C(O)-), alkene, alkyne, phenylene, ether (-O-), thioether (-S-), or amine ($-N(R^a)-$), wherein R^a is defined below. A preferred linkage group is $-C(R_5R_6)-$, wherein R_5 and R_6 are defined above. Suitable substitutents for an alkylene group and a hydrocarbyl group are those which do not substantially interfere with the biloogical activity of the disclosed compounds. R_5 and R_6 are preferred substituents for an alkylene or hydrocarbyl group represented by Y.

An aliphatic group is a straight chained, branched or cyclic non-aromatic hydrocarbon which is completely saturated or which contains one or more units of unsaturation. Typically, a straight chained or branched aliphatic group has from 1 to about 20 carbon atoms, preferably from 1 to about 10, and a cyclic aliphatic group has from 3 to about 10 carbon atoms, preferably from 3 to about 8. An aliphatic group is preferably a straight chained or branched alkyl group, e.g, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *tert*-butyl, pentyl, hexyl, pentyl or octyl, or a cycloalkyl group with 3 to about 8 carbon atoms. A C1-C8 straight chained or branched alkyl group or a C3-C8 cyclic alkyl group is also referred to as a "lower alkyl" group.

The term "aromatic group" may be used interchangeably with "aryl," "aryl ring," "aromatic ring," "aryl group" and "aromatic group." Aromatic groups include carbocyclic aromatic groups such as phenyl, naphthyl, and anthracyl, and heteroaryl groups such as imidazolyl, thienyl, furanyl, pyridyl, pyrimidy, pyranyl, pyrazolyl, pyrroyl, pyrazinyl, thiazole, oxazolyl, and tetrazole. The term "heteroaryl group" may be used interchangeably with "heteroaryl," "heteroaryl ring," "heteroaromatic ring" and "heteroaromatic group." Heteroaryl groups are aromatic groups that comprise one or more heteroatom, such as sulfur, oxygen and nitrogen, in the ring structure. Preferably, heteroaryl groups comprise from one to four heteroatoms.

Aromatic groups also include fused polycyclic aromatic ring systems in which a carbocyclic aromatic ring or heteroaryl ring is fused to one or more other heteroaryl rings. Examples include benzothienyl, benzofuranyl, indolyl, quinolinyl, benzothiazole, benzooxazole, benzimidazole, quinolinyl, isoquinolinyl and isoindolyl.

Non-aromatic heterocyclic rings are non-aromatic rings which include one or more heteroatoms such as nitrogen, oxygen or sulfur in the ring. The ring can be five, six, seven or eight-membered. Preferably, heterocyclic groups comprise from one to about four heteroatoms. Examples include tetrahydrofuranyl, tetrahyrothiophenyl, morpholino, thiomorpholino, pyrrolidinyl, piperazinyl, piperidinyl, and thiazolidinyl.

Suitable substituents on an aliphatic group (including an alkylene group), non-aromatic heterocyclic group, benzylic or aryl group (carbocyclic and heteroaryl) are those which do not substantially interfere with the biological activity of the disclosed compounds. A substituent substantially interferes with biological activity when the biological activity is reduced by more than about 50% in a compound with the substituent compared with a compound without the substituent. Examples of suitable substituents include $-R^a$, -OH, -Br, -Cl, -I, -F, $-OR^a$, $-O-COR^a$, $-COR^a$, -CN, $-NO_2$, -COOH, $-SO_3H$, $-NH_2$, $-NHR^a$, $-N(R^aR^b)$, $-COOR^a$, -CHO, $-CONH_2$, $-CONHR^a$, $-CON(R^aR^b)$, $-NHCOR^a$, $-NR^cCOR^a$, $-NHCONH_2$, $-NHCONR^aH$, $-NHCON(R^aR^b)$, $-NR^cCONH_2$, $-NR^cCONR^aH$, $-NR^cCON(R^aR^b)$, $-C(=NH)-NH_2$, $-C(=NH)-NHR^a$, $-C(=NH)-N(R^aR^b)$, $-C(=NR^c)-NH_2$, $-C(=NR^c)-NHR^a$, $-C(=NR^c)-N(R^aR^b)$, $-NH-C(=NH)-NH_2$, $-NH-C(=NH)-NHR^a$, $-NH-C(=NH)-N(R^aR^b)$, $-NH-C(=NR^c)-NH_2$, $-NH-C(=NR^c)-NHR^a$, $-NH-C(=NR^c)-N(R^aR^b)$, $-NR^dH-C(=NH)-NH_2$, $-NR^d-C(=NH)-NHR^a$, $-NR^d-C(=NH)-N(R^aR^b)$, $-NR^d-C(=NR^c)-NH_2$, $-NR^d-C(=NR^c)-NHR^a$, -

NR^d-C(=NR^c)-N(R^aR^b), -$NHNH_2$, -NHNHR^a, -NHR^aR^b, -SO_2NH_2, -SO_2NHR^a, -$SO_2NR^aR^b$, -CH=CHR^a, -CH=CR^aR^b, -CR^c=CR^aR^b,-CR^c=CHR^a, -CR^c=CR^aR^b, -CCR^a, -SH, -SR^a, -S(O)R^a, -$S(O)_2R^a$.

R^a-R^d are each independently an alkyl group, aromatic group, non-aromatic heterocyclic group or -N(R^aR^b), taken together, form a non-aromatic heterocyclic group. The alkyl, aromatic and non-aromatic heterocyclic group represented by R^a-R^d and the non-aromatic heterocyclic group represented by -N(R^aR^b) are each optionally and independently substituted with one or more groups represented by $R^{\#}$. Preferably R^a-R^d are unsubstituted.

$R^{\#}$ is R^+, -OR^+, -O(haloalkyl), -SR^+, -NO_2, -CN, -NCS, -N(R^+)$_2$, -NHCO_2R^+, -NHC(O)R^+, -NHNHC(O)R^+, -NHC(O)N(R^+)$_2$, -NHNHC(O)N(R^+)$_2$, -NHNHCO_2R^+, -C(O)C(O)R^+, -C(O)CH_2C(O)R^+, -CO_2R^+, -C(O)R^+, -C(O)N(R^+)$_2$, -OC(O)R^+, -OC(O)N(R^+)$_2$, -$S(O)_2R^+$, -SO_2N(R^+)$_2$, -S(O)R^+, -$NHSO_2$N(R^+)$_2$, -$NHSO_2R^+$, -C(=S)N(R^+)$_2$, or -C(=NH)-N(R^+)$_2$.

R^+ is –H, a C1-C4 alkyl group, a monocyclic heteroaryl group, a non-aromatic heterocyclic group or a phenyl group optionally substituted with alkyl, haloalkyl, alkoxy, haloalkoxy, halo, -CN, -NO_2, amine, alkylamine or dialkylamine. Preferably R^+ is unsubstituted. Optionally, the group –N(R^+)$_2$ is a non-aromatic heterocyclic group, provided that non-aromatic heterocyclic groups represented by R^+ and –N(R^+)$_2$ that comprise a secondary ring amine are optionally acylated or alkylated.

Preferred substituents for a phenyl group, including phenyl groups represented by R_1-R_4, include C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy, phenyl, benzyl, pyridyl, -OH, -NH_2, -F, -Cl, -Br, -I, -NO_2 or -CN. More preferred for a phenyl group, including phenyl groups represented by R_1-R_4, include R_1 and R_2 are optionally substituted with -OH, -CN, halogen, C1-4 alkyl or C1-C4 alkoxy

Preferred substituents for a cycloalkyl group, including cycloalkyl groups represented by R_1 and R_2, are alkyl groups, such as a methyl or ethyl group.

In certain embodiments of the present invention the present invention the bis(thiohydrazide amides) described herein can be administered in combination with anti-angiogenesis agents, including, but not limited to, Dalteparin, Suramin, ABT-510, Combretastatin A4 Phosphate, Lenalidomide, LY317615 (Enzastaurin), Soy Isoflavone (Genistein; Soy Protein Isolate), Thalidomide, AMG-706, Anti-VEGF

Antibody (Bevacizumab; Avastin™), AZD2171, Bay 43-9006 (Sorafenib tosylate), PI-88, PTK787/ZK 222584 (Vatalanib), SU11248 (Sunitinib malate), VEGF-Trap, XL184, ZD6474, ATN-161, EMD 121974 (Cilenigtide), Celecoxib, Angiostatin, Endostatin, Regranex, Apligraf, Paclitaxel, tetracyclines, clarithromycin, lasix, captopril, aspirin, Vitamin D3 analogs, retinoids, Imiquomod, Interferon alfa2a, Minocycline, copper peptide containing dressings, LucentisTM, ATG002, Pegaptanib Sodium, Tryptophanyl-tRNA synthetase, squalamine lactate, anecortave acetate, AdPEDF, AG-013958, JSM6427, TG100801, Veglin, ascorbic acid ethers (and their analogs), and Pamidronate.

In one embodiment of the present invention the bis(thiohydrazide amides) described herein can be administered to a subject in the form of a pharmaceutical composition.

As used herein, a "pharmaceutical composition" can be a formulation containing the disclosed compounds, in a form suitable for administration to a subject. The pharmaceutical composition can be in bulk or in unit dosage form. The unit dosage form can be in any of a variety of forms, including, for example, a capsule, an IV bag, a tablet, a single pump on an aerosol inhaler, or a vial. The quantity of active ingredient (i.e., a formulation of the disclosed compound or salts thereof) in a unit dose of composition can be an effective amount and can be varied according to the particular treatment involved. It may be appreciated that it can be necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage can also depend on the route of administration. Examples of suitable dosages are those described in PCT/US2006/014531 filed 13-Apr-2006, titled Combination Cancer Therapy With Bis[Thiohydrazide] Amide Compounds, the entire contents of which are incorporated herein by reference. A variety of routes are contemplated, including topical, oral, pulmonary, rectal, vaginal, parenternal, including transdermal, subcutaneous, intravenous, intramuscular, intraperitoneal and intranasal.

The compounds described herein, and the pharmaceutically acceptable salts thereof can be used in pharmaceutical preparations in combination with a pharmaceutically acceptable carrier or diluent. Suitable pharmaceutically acceptable carriers include inert solid fillers or diluents and sterile aqueous or organic solutions.

The compounds can be present in such pharmaceutical compositions in amounts sufficient to provide the desired dosage amount in the range described herein. Techniques for formulation and administration of the disclosed compounds of the invention can be found in *Remington: the Science and Practice of Pharmacy*, 19th edition, Mack Publishing Co., Easton, PA (1995). The bis(thio-hydrazide amide) disclosed herein can be prepared by the methods described in U.S. Provisional Patent No.: 60/708,977 filed 16-Aug-2005, titled Bis(Thio-Hydrazide Amide) Formulation, the entire teachings of which is incorporated herein by reference.

For oral administration, the disclosed compounds or salts thereof can be combined with a suitable solid or liquid carrier or diluent to form capsules, tablets, pills, powders, syrups, solutions, suspensions, or the like.

The tablets, pills, capsules, and the like can contain from about 1 to about 99 weight percent of the active ingredient and a binder such as gum tragacanth, acacias, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch or alginic acid; a lubricant such as magnesium stearate; and/or a sweetening agent such as sucrose, lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Various other materials can be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor, and the like.

For parental administration, the bis(thio-hydrazide) amides can be combined with sterile aqueous or organic media to form injectable solutions or suspensions. For example, solutions in sesame or peanut oil, aqueous propylene glycol and the like can be used, as well as aqueous solutions of water-soluble pharmaceutically-acceptable salts of the compounds. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

In addition to the formulations previously described, the compounds may also be formulated as a depot preparation. Suitable formulations of this type include biocompatible and biodegradable polymeric hydrogel formulations using crosslinked or water insoluble polysaccharide formulations, polymerizable polyethylene oxide formulations, impregnated membranes, and the like. Such long acting formulations may be administered by implantation or transcutaneous delivery (for example subcutaneously or intramuscularly), intramuscular injection or a transdermal patch. Typically, they can be implanted in, or applied to, the microenvironment of an affected organ or tissue, for example, a membrane impregnated with the disclosed compound can be applied to an open wound or burn injury. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials, for example, as an emulsion in an acceptable oil, or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For topical administration, suitable formulations may include biocompatible oil, wax, gel, powder, polymer, or other liquid or solid carriers. Such formulations may be administered by applying directly to affected tissues, for example, a liquid formulation to treat infection of conjunctival tissue can be administered dropwise to the subject's eye, a cream formulation can be administer to a wound site, or a bandage may be impregnated with a formulation, and the like.

For rectal administration, suitable pharmaceutical compositions are, for example, topical preparations, suppositories or enemas.

For vaginal administration, suitable pharmaceutical compositions are, for example, topical preparations, pessaries, tampons, creams, gels, pastes, foams or sprays.

In addition, the compounds may also be formulated to deliver the active agent by pulmonary administration, e.g., administration of an aerosol formulation containing the active agent from, for example, a manual pump spray, nebulizer or pressurized metered-dose inhaler. Suitable formulations of this type can also include other agents, such as antistatic agents, to maintain the disclosed compounds as effective aerosols.

The term "pulmonary" as used herein refers to any part, tissue or organ whose primary function is gas exchange with the external environment, i.e., O_2/CO_2

exchange, within a patient. "Pulmonary" typically refers to the tissues of the respiratory tract. Thus, the phrase "pulmonary administration" refers to administering the formulations described herein to any part, tissue or organ whose primary function is gas exchange with the external environment (e.g., mouth, nose, pharynx, oropharynx, laryngopharynx, larynx, trachea, carina, bronchi, bronchioles, alveoli). For purposes of the present invention, "pulmonary" is also meant to include a tissue or cavity that is contingent to the respiratory tract, in particular, the sinuses.

A drug delivery device for delivering aerosols can comprise a suitable aerosol canister with a metering valve containing a pharmaceutical aerosol formulation as described and an actuator housing adapted to hold the canister and allow for drug delivery. The canister in the drug delivery device has a head space representing greater than about 15% of the total volume of the canister. Often, the polymer intended for pulmonary administration is dissolved, suspended or emulsified in a mixture of a solvent, surfactant and propellant. The mixture is maintained under pressure in a canister that has been sealed with a metering valve.

For nasal administration, either a solid or a liquid carrier can be used. The solid carrier includes a coarse powder having particle size in the range of, for example, from about 20 to about 500 microns and such formulation is administered by rapid inhalation through the nasal passages. Where the liquid carrier is used, the formulation may be administered as a nasal spray or drops and may include oil or aqueous solutions of the active ingredients.

In addition to the formulations described above, a formulation can optionally include, or be co-administered with one or more additional drugs. The formulation may also contain preserving agents, solubilizing agents, chemical buffers, surfactants, emulsifiers, colorants, odorants and sweeteners.

A "subject" is a mammal, preferably a human, but can also be an animal in need of veterinary treatment, e.g., companion animals (e.g., dogs, cats, and the like), farm animals (e.g., cows, sheep, pigs, horses, and the like) and laboratory animals (e.g., rats, mice, guinea pigs, and the like).

The term "effective amount" is the quantity of compound in which a beneficial clinical outcome is achieved when the compound is administered to a subject in need thereof. A "beneficial clinical outcome" includes a partial or significant reduction in

formation of blood vessels; a reduction in the severity of the symptoms associated with the condition and/or an increase in the longevity of the subject compared with the absence of the treatment. The precise amount of compound (or other therapeutic agent) administered to a subject will depend on the type and severity of the disease or condition and on the characteristics of the subject, such as general health, age, sex, body weight and tolerance to drugs. It will also depend on the degree, severity and type of condition. The skilled artisan will be able to determine appropriate dosages depending on these and other factors. Effective amounts of the disclosed compounds typically range between about 10 g/kg per day to about 1 mg/kg per day, 5 g/kg per day to about 5 mg/kg per day, 3 g/kg per day to about 10 mg/kg per day 2 g/kg per day to about 50 mg/kg per day. When co-administered with another therapeutic agent, an "effective amount" of the therapeutic agent will depend on the type of drug used.

The bis(thio-hydrazide amide) disclosed herein can be prepared by the methods described in U.S. Publication Nos. 20060135595, 2003/0045518 and 2003/0119914, U.S. Application Serial No.: 11/432,307, filed 11-May-2006, titled Synthesis Of Bis(Thio-Hydrazide Amide) Salts, U.S. Provisional Patent No.: 60/708,977 filed 16-Aug-2005, titled Bis(Thio-Hydrazide Amide) Formulation and also according to methods described in U.S. Publication No. 2004/0225016 A1, entitled TREATMENT FOR CANCERS. The entire teachings of these applications are incorporated herein by reference.

The present invention is illustrated by the following examples, which are not intended to be limiting in any way.

EXEMPLIFICATION

Example 1, Inhibition of HUVEC cell migration

To examine if the compounds of the invention affect endothelial cell function, an *in vitro* human umbilical vein endothelial cell (HUVEC) migration assay is performed in the presence of a compound of the invention. HUVEC cells (passage number 4) are cultured on 12-well plates and time-lapse imaging is performed with the live cell imaging system on an inverted microscope supplied with 6-7% CO_2. The

temperature is kept at 37°C. Images are taken every 30 minutes using the 2X objective for up to 106 hr or every 60 seconds using the 20X objective for 30 min. Confluent HUVEC cultures are scraped similarly to make a blank area, followed by culturing in HUVEC medium for 15 hr without treatment. The migration areas, which are imaged as time-lapse sequences for each well, are used as a basis to standardize/correct migration rates. Then, migration of cells under different treatments is imaged at the same time to generate time-lapse image sequences for each well. Time-lapse movies are further analyzed by measuring areas that are covered by migrating cells. During experiments, HUVEC cells are activated by the presence of VEGF and basic FGF. Compounds of the invention (*e.g.* 100 nM and 1 μM) are expected to completely block migration of HUVEC cells to the blank area, indicating that compounds of the invention possesses potent inhibitory effect on the migration of activated HUVEC cell *in vitro* induced by VEGF and basic FGF.

It is also possible to track HUVEC behavior during above treatments. It is expected that HUVEC cells will begin to shrink after 24 hr treatment with compounds of the invention.

Example 2, Enhanced VE-cadherin junctions of HUVEC cells

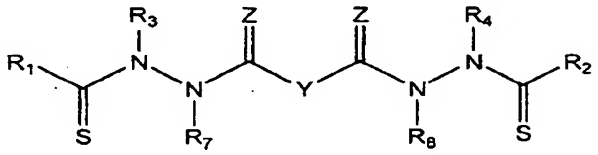
An immunofluoscence study is performed by using anti-VE-cadherin antibodies to examine VE-cadherin junctions between HUVEC cells. HUVEC cells are treated with DMSO or a compound of the invention (*e.g.* 10, 100 and 1000nM) for 24 hrs and fixed for immunostaining. DMSO concentration is 1:100 for all treatments. To boost the immunofluorescence signal, cells are stained with a mixture of 2 polyclonal anti-human VE-cadherin Abs followed by staining with a mixture of fluorescent secondary antibodies. It is expected that with compounds of the invention, VE-cadherin staining will be extremely strong in cell-cell junction regions, but not the non-contacted regions compared to that in DMSO treated cultures. Compounds of the invention are expected to enhance the assembly of cell-cell junctions of activated human endothelial cells, likely through induction of the accumulation of VE-cadherin molecules at the junctions. This effect could result in limited motility of the cells and reducing permeability of the endothelium, thus contributing to the cell migration inhibition and the potential anti-angiogenesis effect of compounds of the invention.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

What is claimed is:

1. A method of inhibiting angiogenesis in a subject in need thereof, comprising administering to the subject an effective amount of a compound represented by the following Structural Formula:



or a pharmaceutically acceptable salt or solvate thereof, wherein:

Y is a covalent bond or an optionally substituted straight chained hydrocarbyl group, or, Y, taken together with both >C=Z groups to which it is bonded, is an optionally substituted aromatic group;

R_1-R_4 are independently -H, an optionally substituted aliphatic group, an optionally substituted aryl group, or R_1 and R_3 taken together with the carbon and nitrogen atoms to which they are bonded, and/or R_2 and R_4 taken together with the carbon and nitrogen atoms to which they are bonded, form a non-aromatic heterocyclic ring optionally fused to an aromatic ring;

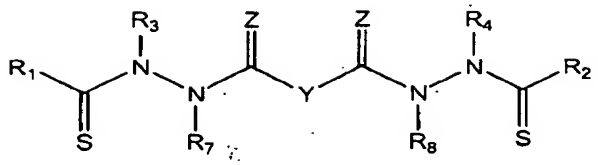
R_7-R_8 are independently -H, an optionally substituted aliphatic group, or an optionally substituted aryl group; and

Z is O or S;

with the proviso that the subject does not suffer from a condition selected from the group consisting of diabetic retinopathy, retinopathy of prematurity, systemic lupus, mycobacteria infections, bacterial ulcers; fungal ulcers; Herpes simplex infections; Herpes zoster infections; protozoan infections, toxoplasmosis diseases caused by the abnormal proliferation of fibrovascular or fibrous tissue including all forms of proliferative vitreoretinopathy, interstitial pulmonary fibrosis, eczema; syphilis, Kaposi's sarcoma, trauma, trauma and post-laser complications; artery occlusion, atherosclerosis; endometriosis, wound healing, ulcers (Helicobacter pylori),

Mooren's ulcer; periodontal disease, hepatitis, rhinitis, bronchitis, pneumonia and cancer.

2. A method of treating a subject with a condition selected from the group consisting of ocular neovascular disease, macular degeneration (e.g., age-related); corneal graft rejection; neovascular glaucoma; retrolental fibroplasias; epidemic keratoconjunctivitis; Vitamin A deficiency; contact lens overwear; atopic keratitis; superior limbic keratitis; pterygium keratitis sicca; sjogrens; acne; rosacea; wartsphylectenulosis; lipid degeneration; chemical burns; Terrien's marginal degeneration; mariginal keratolysis; rheumatoid arthritis; polyarteritis; Wegener's sarcoidosis; scleritis; Stevens-Johnson disease; pemphigoid; radial keratotomy; corneal graph rejection; sickle cell anemia; sarcoid; pseudoxanthoma elasticum; Paget's disease; vein occlusion; carotid obstructive disease; chronic uveitis/vitritis; Eales' disease; Behcet's disease; infections causing a retinitis or choroiditis; presumed ocular histoplasmosis; Best's disease; myopia; optic pits; Stargardt's disease; pars planitis; chronic retinal detachment; hyperviscosity syndromes; diseases associated with rubeosis (neovascularization of the angle); osteoarthritis; ulcerative colitis; Crohn's disease; BartonellosisOsler-Weber-Rendu disease; hereditary hemorrhagic telangiectasia; pulmonary hemangiomatosis; pre-eclampsia; fibrosis of the liver and of the kidney; developmental abnormalities (organogenesis); skin discloloration (*e.g.*, hemangioma, nevus flammeus, or nevus simplex); hypertrophic scars, *i.e.*, keloids; wound granulation; vascular adhesions; cat scratch disease (Rochele ninalia quintosa); keratoconjunctivitis; gingivitis; epulis; tonsillitis; obesity; laryngitis; tracheitis; bronchiolitis; pulmonary edema; neurodermitis; thyroiditis; thyroid enlargement; glomerulonephritis; gastritis; inflammatory bone and cartilage destruction; thromboembolic disease; and Buerger's disease, comprising administering to the subject an effective amount of a compound represented by the following Structural Formula:



or a pharmaceutically acceptable salt or solvate thereof, wherein:

Y is a covalent bond or an optionally substituted straight chained hydrocarbyl group, or, Y, taken together with both >C=Z groups to which it is bonded, is an optionally substituted aromatic group;

R_1-R_4 are independently -H, an optionally substituted aliphatic group, an optionally substituted aryl group, or R_1 and R_3 taken together with the carbon and nitrogen atoms to which they are bonded, and/or R_2 and R_4 taken together with the carbon and nitrogen atoms to which they are bonded, form a non-aromatic heterocyclic ring optionally fused to an aromatic ring;

R_7-R_8 are independently -H, an optionally substituted aliphatic group, or an optionally substituted aryl group; and

Z is O or S.

3. The method of Claim 2 wherein Z is O, R_1 and R_2 are the same and R_3 and R_4 are the same.

4. The method of Claim 3, wherein:

Y is a covalent bond, -C(R_5R_6)-, -(CH_2CH_2)-, *trans*-(CH=CH)-, *cis*-(CH=CH)- or -(C≡ C)-; and

R_5 and R_6 are each independently -H, an aliphatic or substituted aliphatic group, or R_5 is -H and R_6 is an optionally substituted aryl group, or, R_5 and R_6, taken together, are an optionally substituted C2-C6 alkylene group.

5. The method of Claim 4, wherein:

Y is -C(R_5R_6)-;

R_1 and R_2 are each an optionally substituted aryl group; and

R_3 and R_4 are each an optionally substituted aliphatic group.

6. The method of Claim 5, wherein R_5 is -H and R_6 is -H, an aliphatic or substituted aliphatic group.

7. The method of Claim 6, wherein R_3 and R_4 are each an alkyl group optionally substituted with -OH, halogen, phenyl, benzyl, pyridyl, or C1-C8 alkoxy and R_6 is -H or methyl.

8. The method of Claim 7, wherein R_1 and R_2 are each an optionally substituted phenyl group.

9. The method of Claim 8, wherein the phenyl group represented by R_1 and the phenyl group represented by R_2 are optionally substituted with one or more groups selected from: -R^a, -OH, -Br, -Cl, -I, -F, -OR^a, -O-COR^a, -COR^a, -CN, -NCS, -NO_2, -COOH, -SO_3H, -NH_2, -NHR^a, -$N(R^aR^b)$, -$COOR^a$, -CHO, -$CONH_2$, -$CONHR^a$, -$CON(R^aR^b)$, -$NHCOR^a$, -NR^cCOR^a, -$NHCONH_2$, -$NHCONR^aH$, -$NHCON(R^aR^b)$, -NR^cCONH_2, -NR^cCONR^aH, -$NR^cCON(R^aR^b)$, -C(=NH)-NH_2, -C(=NH)-NHR^a, -C(=NH)-$N(R^aR^b)$, -$C(=NR^c)$-NH_2, -$C(=NR^c)$-NHR^a, -$C(=NR^c)$-$N(R^aR^b)$, -NH-C(=NH)-NH_2, -NH-C(=NH)-NHR^a, -NH-C(=NH)-$N(R^aR^b)$, -NH-$C(=NR^c)$-NH_2, -NH-$C(=NR^c)$-NHR^a, -NH-$C(=NR^c)$-$N(R^aR^b)$, -NR^d-C(=NH)-NH_2, -NR^d-C(=NH)-NHR^a, -NR^d-C(=NH)-$N(R^aR^b)$, -NR^d-$C(=NR^c)$-NH_2, -NR^d-$C(=NR^c)$-NHR^a, -NR^d-$C(=NR^c)$-$N(R^aR^b)$, -$NHNH_2$, -$NHNHR^a$, -$NHNR^aR^b$, -SO_2NH_2, -SO_2NHR^a, -$SO_2NR^aR^b$, -CH=CHR^a, -CH=CR^aR^b, -CR^c=CR^aR^b, -CR^c=CHR^a, -CR^c=CR^aR^b, -CCR^a, -SH, -SR^a, -$S(O)R^a$, -$S(O)_2R^a$, wherein R^a-R^d are each independently an alkyl group, aromatic group, non-aromatic heterocyclic group; or, -$N(R^aR^b)$, taken together, form an optionally substituted non-aromatic heterocyclic group, wherein the alkyl, aromatic and non-aromatic heterocyclic group represented by R^a-R^d and the non-aromatic heterocyclic group represented by -$N(R^aR^b)$ are each optionally and independently substituted with one or more groups represented by $R^{\#}$, wherein $R^{\#}$ is R^+, -OR^+, -O(haloalkyl), -SR^+, -NO_2, -CN,

-NCS, -$N(R^+)_2$, -$NHCO_2R^+$, -$NHC(O)R^+$, -$NHNHC(O)R^+$, -$NHC(O)N(R^+)_2$, -$NHNHC(O)N(R^+)_2$, -$NHNHCO_2R^+$, -$C(O)C(O)R^+$, -$C(O)CH_2C(O)R^+$, -CO_2R^+, -$C(O)R^+$, $C(O)N(R^+)_2$, -$OC(O)R^+$, -$OC(O)N(R^+)_2$, -$S(O)_2R^+$, -$SO_2N(R^+)_2$, -$S(O)R^+$, -$NHSO_2N(R^+)_2$, -$NHSO_2R^+$, -$C(=S)N(R^+)_2$, or -$C(=NH)$-$N(R^+)_2$; wherein R^+ is –H, a C1-C4 alkyl group, a monocyclic heteroaryl group, a non-aromatic heterocyclic group or a phenyl group optionally substituted with alkyl, haloalkyl, alkoxy, haloalkoxy, halo, -CN, -NO_2, amine, alkylamine or dialkylamine; or $–N(R^+)_2$ is a non-aromatic heterocyclic group, provided that non-aromatic heterocyclic groups represented by R^+ and $–N(R^+)_2$ that comprise a secondary ring amine are optionally acylated or alkylated.

10. The method of Claim 9, wherein the phenyl groups represented by R_1 and R_2 are optionally substituted with C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy, phenyl, benzyl, pyridyl, -OH, -NH_2, -F, -Cl, -Br, -I, -NO_2 or -CN.

11. The method of Claim 10, wherein the phenyl groups represented by R_1 and R_2 are optionally substituted with -OH, -CN, halogen, C1-4 alkyl or C1-C4 alkoxy and R_3 and R_4 are each methyl or ethyl optionally substituted with -OH, halogen or C1-C4 alkoxy.

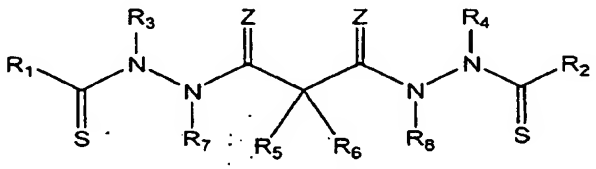
12. The method of Claim 4, wherein:
Y is -CR_5R_6-;
R_1 and R_2 are both an optionally substituted aliphatic group;
R_5 is -H; and
R_6 is -H or an optionally substituted aliphatic group.

13. The method of Claim 12, wherein R_1 and R_2 are both a C3-C8 cycloalkyl group optionally substituted with at least one alkyl group.

14. The method of Claim 13, wherein R_3 and R_4 are both an alkyl group optionally substituted with -OH, halogen, phenyl, benzyl, pyridyl, or C1-C8 alkoxy; and R_6 is -H or methyl.

15. The method of Claim 14, wherein R_1 and R_2 are both cyclopropyl or 1-methylcyclopropyl.

16. The method of Claim 2, wherein the compound is represented by the following Structural Formula:



or a pharmaceutically acceptable salt or solvate thereof, wherein:

R_7-R_8 are both -H, and:

R_1 and R_2 are both phenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H;

R_1 and R_2 are both phenyl, R_3 and R_4 are both ethyl, and R_5 and R_6 are both -H;

R_1 and R_2 are both 4-cyanophenyl, R_3 and R_4 are both methyl, R_5 is methyl, and R_6 is -H;

R_1 and R_2 are both 4-methoxyphenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H;

R_1 and R_2 are both phenyl, R_3 and R_4 are both methyl, R_5 is methyl, and R_6 is -H;

R_1 and R_2 are both phenyl, R_3 and R_4 are both ethyl, R_5 is methyl, and R_6 is -H;

R_1 and R_2 are both 4-cyanophenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H;

R_1 and R_2 are both 2,5-dimethoxyphenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H;

R_1 and R_2 are both 2,5-dimethoxyphenyl, R_3 and R_4 are both methyl, R_5 is methyl, and R_6 is -H;

R_1 and R_2 are both 3-cyanophenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H;

R_1 and R_2 are both 3-fluorophenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H;

R_1 and R_2 are both 4-chlorophenyl, R_3 and R_4 are both methyl, R_5 is methyl, and R_6 is -H;

R_1 and R_2 are both 2-dimethoxyphenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H;

R_1 and R_2 are both 3-methoxyphenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H;

R_1 and R_2 are both 2,3-dimethoxyphenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H;

R_1 and R_2 are both 2,3-dimethoxyphenyl, R_3 and R_4 are both methyl, R_5 is methyl, and R_6 is -H;

R_1 and R_2 are both 2,5-difluorophenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H;

R_1 and R_2 are both 2,5-difluorophenyl, R_3 and R_4 are both methyl, R_5 is methyl, and R_6 is -H;

R_1 and R_2 are both 2,5-dichlorophenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H;

R_1 and R_2 are both 2,5-dimethylphenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H;

R_1 and R_2 are both 2,5-dimethoxyphenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H;

R_1 and R_2 are both phenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H;

R_1 and R_2 are both 2,5-dimethoxyphenyl, R_3 and R_4 are both methyl, R_5 is methyl, and R_6 is -H;

R_1 and R_2 are both cyclopropyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H;

R_1 and R_2 are both cyclopropyl, R_3 and R_4 are both ethyl, and R_5 and R_6 are both -H;

R_1 and R_2 are both cyclopropyl, R_3 and R_4 are both methyl, R_5 is methyl, and R_6 is -H;

R_1 and R_2 are both 1-methylcyclopropyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H;

R_1 and R_2 are both 1-methylcyclopropyl, R_3 and R_4 are both methyl, R_5 is methyl and R_6 is -H;

R_1 and R_2 are both 1-methylcyclopropyl, R_3 and R_4 are both methyl, R_5 is ethyl, and R_6 is -H;

R_1 and R_2 are both 1-methylcyclopropyl, R_3 and R_4 are both methyl, R_5 is *n*-propyl, and R_6 is -H;

R_1 and R_2 are both 1-methylcyclopropyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both methyl;

R_1 and R_2 are both 1-methylcyclopropyl, R_3 and R_4 are both ethyl, and R_5 and R_6 are both -H;

R_1 and R_2 are both 1-methylcyclopropyl, R_3 is methyl, R_4 is ethyl, and R_5 and R_6 are both -H;

R_1 and R_2 are both 2-methylcyclopropyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H;

R_1 and R_2 are both 2-phenylcyclopropyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H;

R_1 and R_2 are both 1-phenylcyclopropyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H;

R_1 and R_2 are both cyclobutyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H;

R_1 and R_2 are both cyclopentyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H;

R_1 and R_2 are both cyclohexyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H;

R_1 and R_2 are both cyclohexyl, R_3 and R_4 are both phenyl, and R_5 and R_6 are both -H;

R_1 and R_2 are both methyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H;

R_1 and R_2 are both methyl, R_3 and R_4 are both *t*-butyl, and R_5 and R_6 are both -H;

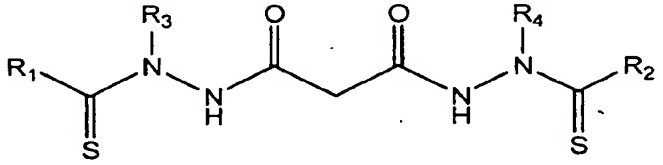
R_1 and R_2 are both methyl, R_3 and R_4 are both phenyl, and R_5 and R_6 are both -H;

R_1 and R_2 are both *t*-butyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H;

R_1 and R_2 are ethyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; or

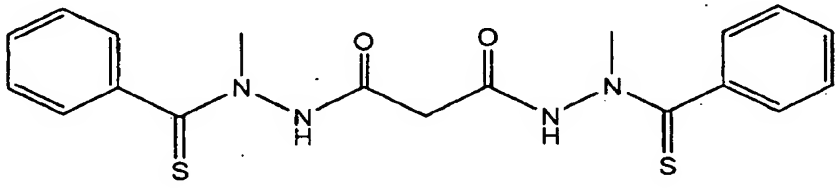
R_1 and R_2 are both *n*-propyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H.

17. The method of Claim 2, wherein the compound is represented by the following Structural Formula:

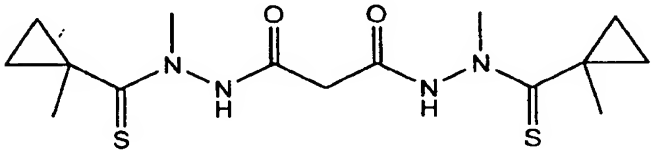


or a pharmaceutically acceptable salt thereof.

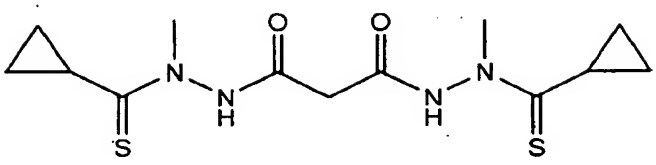
18. The method of Claim 17, wherein the compound is represented by one of the following Structural Formulas:



;

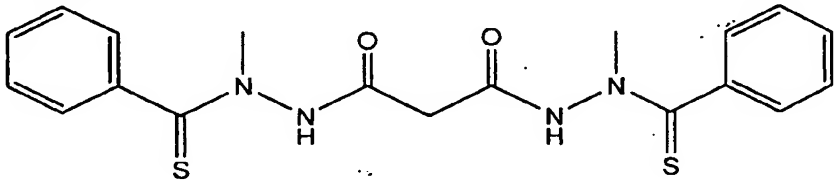


; and



or a pharmaceutically acceptable salt thereof.

19. The method of Claim 18, wherein the compound is represented by the following Structural Formula:



or a pharmaceutically acceptable salt thereof.

20. The method of any one of Claims 1-18, wherein the subject is human.

21. The method of any one of Claims 1-18, wherein the compound is administered as a monotherapy.

22. The method of any one of Claims 1-18, wherein the compound is a disodium or a dipotassium salt.

23. The method of any one of Claims 1-18, wherein the subject is suffering from sprouting angiogenesis.

24. The method of any one of Claims 1-18, wherein the subject is suffering from
intussusceptive angiogenesis.

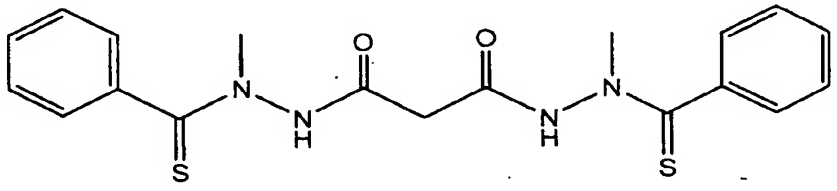
25. The method of any one of Claims 1-18 wherein the subject is suffering from rheumatoid arthritis.

26. The method of any one of Claims 1-18 wherein the subject is suffering from osteoarthritis.

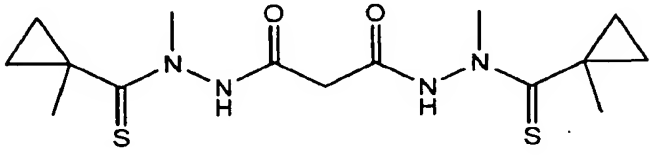
27. The method of any one of Claims 1-18 wherein the subject is suffering from Crohn's disease.

28. The method of any one of Claims 1-18 wherein the subject is suffering from obesity.

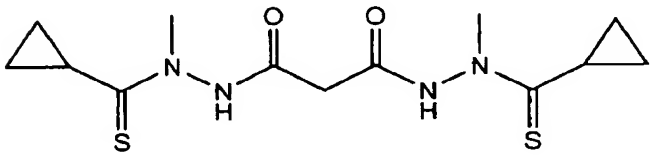
29. A method of inhibiting angiogenesis in a subject in need thereof, comprising administering to the subject an effective amount of a compound represented by a Structural Formula selected from:



;



; and



,

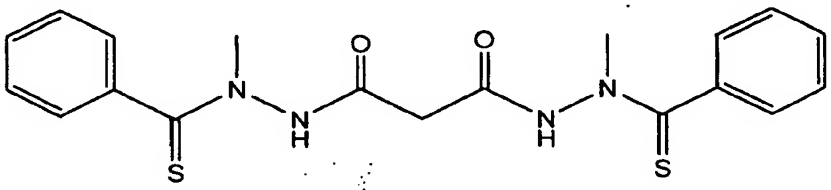
or a pharmaceutically acceptable salt thereof;

with the proviso that the subject does not suffer from a condition selected from the group consisting of diabetic retinopathy, retinopathy of

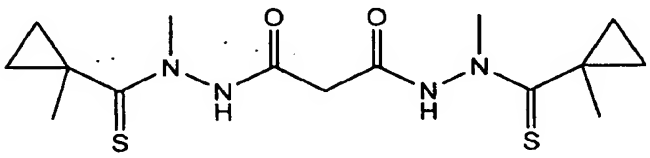
prematurity, systemic lupus, mycobacteria infections, bacterial ulcers; fungal ulcers; Herpes simplex infections; Herpes zoster infections; protozoan infections, toxoplasmosis diseases caused by the abnormal proliferation of fibrovascular or fibrous tissue including all forms of proliferative vitreoretinopathy, interstitial pulmonary fibrosis, eczema; syphilis, Kaposi's sarcoma, trauma, trauma and post-laser complications; artery occlusion, atherosclerosis; endometriosis, wound healing, ulcers (Helicobacter pylori), Mooren's ulcer; periodontal disease, hepatitis, rhinitis, bronchitis, and pneumonia.

30. A method of treating a subject with a condition selected from the group consisting of ocular neovascular disease, macular degeneration (e.g., age-related); corneal graft rejection; neovascular glaucoma; retrolental fibroplasias; epidemic keratoconjunctivitis; Vitamin A deficiency; contact lens overwear; atopic keratitis; superior limbic keratitis; pterygium keratitis sicca; sjogrens; acne; rosacea; wartsphylectenulosis; lipid degeneration; chemical burns; Terrien's marginal degeneration; mariginal keratolysis; rheumatoid arthritis; polyarteritis; Wegener's sarcoidosis; scleritis; Stevens-Johnson disease; pemphigoid; radial keratotomy; corneal graph rejection; sickle cell anemia; sarcoid; pseudoxanthoma elasticum; Paget's disease; vein occlusion; carotid obstructive disease; chronic uveitis/vitritis; Eales' disease; Behcet's disease; infections causing a retinitis or choroiditis; presumed ocular histoplasmosis; Best's disease; myopia; optic pits; Stargardt's disease; pars planitis; chronic retinal detachment; hyperviscosity syndromes; diseases associated with rubeosis (neovascularlariation of the angle); osteoarthritis; ulcerative colitis; Crohn's disease; BartonellosisOsler-Weber-Rendu disease; hereditary hemorrhagic telangiectasia; pulmonary hemangiomatosis; pre-eclampsia; fibrosis of the liver and of the kidney; developmental abnormalities (organogenesis); skin disclolorations (*e.g.*, hemangioma, nevus flammeus, or nevus simplex); hypertrophic scars, *i.e.*, keloids; wound granulation; vascular adhesions; cat scratch disease (Rochele ninalia quintosa); keratoconjunctivitis; gingivitis; epulis; tonsillitis; obesity;

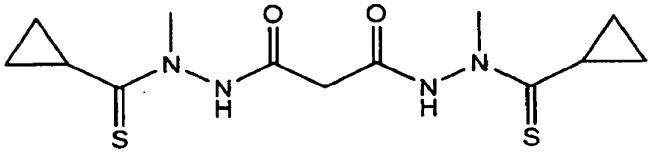
laryngitis; tracheitis; bronchiolitis; pulmonary edema; neurodermitis; thyroiditis; thyroid enlargement; glomerulonephritis; gastritis; inflammatory bone and cartilage destruction; thromboembolic disease; and Buerger's disease, comprising administering to the subject an effective amount of a compound represented by a Structural Formula selected from:



;



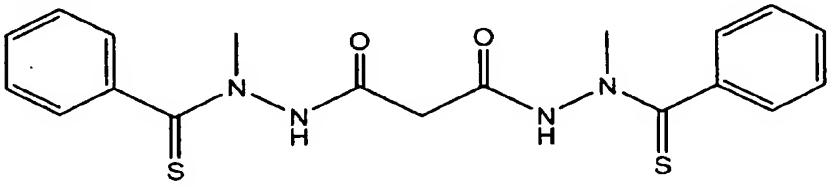
; and



,

or a pharmaceutically acceptable salt thereof.

31. The method of Claim 30, wherein the compound is represented by the following Structural Formula:



or a pharmaceutically acceptable salt thereof.

32. The method of Claim 31, wherein the subject is human.

33. The method of Claim 32, wherein the compound is a disodium or a dipotassium salt.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/018353

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/16 A61K31/165 A61P43/00 A61P19/02 A61P1/00
A61P3/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2006/113572 A (SYNTA PHARMACEUTICALS CORP [US]; BARSOUM JAMES [US]; DU ZHENJIAN [US]) 26 October 2006 (2006-10-26) abstract page 4, line 19 - page 14, line 4 page 28, line 12 - line 27 page 29, line 23 - page 30, line 5; claims 1-3,21-30	1-24, 29-33
X	WO 2006/062732 A (SYNTA PHARMACEUTICALS CORP [US]; ZHANG MEI [US]; LADANYI ANDRAS [HU]) 15 June 2006 (2006-06-15) abstract page 2, line 10 - page 4, line 4 page 22, line 17 - page 34, line 8 page 43, line 22 - page 44, line 8 page 45, line 4 - page 46, line 20; claims 28,37-39	1-26, 29-33

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 January 2008	21/01/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hoff, Philippe

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/018353

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/033913 A (SYNTA PHARMACEUTICALS CORP [US]; VAGHEFI FARID [US]; CHEN LAN BO [US];) 30 March 2006 (2006-03-30) abstract page 2, line 5 - page 3, line 19 page 7, line 10 - page 17, line 6; claims 1-7,32-36	1-24, 29-33
X	WO 2006/055747 A (SYNTA PHARMACEUTICALS CORP [US]; BARSOUM JAMES [US]) 26 May 2006 (2006-05-26) abstract page 3, line 18 - page 17, line 8 page 18, line 13 - line 22; claims; example 4	2-24, 30-33
A	CARMELIET PETER: "Angiogenesis in health and disease" NATURE MEDICINE, NATURE PUBLISHING GROUP, NEW YORK, NY, US, vol. 9, no. 6, June 2003 (2003-06), pages 653-660, XP002422112 ISSN: 1078-8956 the whole document	1-33
A	WO 2004/064826 A (SYNTA PHARMACEUTICALS CORP [US]; KOYA KEIZO [US]; SUN LIJUN [US]; WU Y) 5 August 2004 (2004-08-05) abstract; claims; examples	1-33

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/018353

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-33 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

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